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Short Communication

Telavancin activity when tested by a revised susceptibility testing method against uncommonly isolated Gram-positive pathogens responsible for documented infections in hospitals worldwide (2011–2013)

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ABSTRACT

The broth microdilution method for telavancin susceptibility testing was revised and now utilises DMSO as solvent for stock solution preparation and diluent for stock solution dilution, following CLSI guidelines for water-insoluble agents. The revised method also incorporates polysorbate 80 in the test medium to mitigate drug binding to plastics. This revised methodology provides more accurate and reproducible MIC determinations, which results in values lower than the previously established method. This study was conducted to re-establish telavancin potencies and susceptibility profiles (using updated interpretive criteria) against a collection of uncommon clinical pathogens (3821 isolates). Telavancin showed MIC_{50} values of 0.06 mg/L against tested staphylococcal species ($MIC_{50/90}$, 0.03/0.06 mg/L; 98.1–100.0% susceptible), with lower results for *Staphylococcus hominis* (MIC_{50}, ≤0.015 mg/L), *Staphylococcus lugdunensis* (MIC_{50}, ≤0.015 mg/L) and *Staphylococcus simulans* (MIC_{50}, 0.03 mg/L). Vancomycin (MIC_{50}, 1 mg/L), daptomycin (MIC_{50}, 0.12–1 mg/L) and linezolid (MIC_{50}, 0.25–1 mg/L) had MIC_{50} results at least four-fold higher than telavancin against CoNS. Streptococci (99.2–100.0% susceptible) displayed telavancin MIC_{50} values of ≤0.015–0.03 mg/L. Vancomycin (MIC_{50}, 0.25–0.5 mg/L) and linezolid (MIC_{50}, 0.5–1 mg/L) had higher MIC_{50} results against streptococci, whilst daptomycin MIC_{50} values varied from ≤0.06 mg/L to 0.5 mg/L. *Micrococcus*, *Listeria* and *Corynebacterium* spp. were inhibited by telavancin at ≤0.015, ≤0.03 and ≤0.06 mg/L, respectively. Telavancin exhibited potent in vitro activity against this collection, greater than comparators (daptomycin, linezolid, vancomycin). This study provides new baseline MIC results for telavancin and confirms the spectrum and potency of telavancin against less commonly encountered Gram-positive species.

1. Introduction

Telavancin was approved in 2009 in North America (USA and Canada) for the treatment of adults with complicated skin and soft-tissue infections (cSSTI) caused by susceptible organisms. In addition, it was granted approval in the USA and Europe for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia caused by susceptible isolates of *Staphylococcus aureus* [meticillin-resistant *S. aureus* (MRSA) only in Europe] when alternative treatments are not suitable [1]. Telavancin possesses concentration-dependent bactericidal activity due to a dual mechanism of action combining inhibition of cell wall synthesis and disruption of bacterial cell membrane function [2]. These mechanisms of action provide potent antimicrobial activity for telavancin against a broad range of Gram-positive organisms, which has been reported in several previous studies [3–6].

Broth microdilution susceptibility testing method for telavancin was revised to accommodate modifications associated with preparation of telavancin stock solution and dilution, which now follow the current Clinical and Laboratory Standards Institute (CLSI) guidelines for water-insoluble agents [7,8]. Moreover, this revised method also includes the addition of 0.002% polysorbate 80 to the test medium, which has been shown to reduce the binding of

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lipoglycopeptides to plastics [7]. This revised broth microdilution method was approved by the CLSI [9] and the US Food and Drug Administration (FDA) [1]. This revised method provides more accurate, precise and reproducible telavancin minimum inhibitory concentration (MIC) determinations; however, these results are lower than those obtained by the previously established method [7,8]. Therefore, this study was performed to establish the activity and spectrum of telavancin when using a revised microdilution method tested against a worldwide collection of rarely isolated clinical pathogens.

2. Materials and methods

2.1. Bacterial strains

A total of 3821 consecutive, non-duplicate, Gram-positive clinical isolates were included in this study, which were collected from medical centers located in 12 countries in the Asia-Western Pacific region (35 sites), 21 countries in Europe and Israel (53 sites), 11 countries in Latin America (21 sites) and 2 countries in North America (110 sites). These isolates were recovered primarily from bacteraemia (44%), SSTI (28%) and respiratory tract infections (8%), deemed clinically relevant by local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA) as part of the SENTRY Antimicrobial Surveillance Program for 2011–2013. Isolates were initially identified by the participating laboratory and the identification was confirmed by the reference monitoring laboratory (JMI Laboratories) using standard algorithms and supported by VITEK® 2 (bioMérieux, Hazelwood, MO) and matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Daltonics, Bremen, Germany).

2.2. Antimicrobial susceptibility profile

Isolates were tested for susceptibility by broth microdilution following the guidelines in CLSI document M07-A9 [10]. Testing was performed using dry-form panels manufactured by Thermo Fisher Scientific (Cleveland, OH). These panels were previously validated and shown to provide MIC results equivalent to the revised, and CLSI- and FDA-approved, broth microdilution method (supplemented with 0.002% polysorbate 80) described above [7]. Bacterial inoculum density was monitored by colony counts to assure an adequate number of cells for each testing event. Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619) [9]. All quality control results were within published acceptable ranges. The FDA-approved breakpoint for *S. aureus* (≤0.12 mg/L) was applied to coagulase-negative staphylococci (CoNS) [1]. The breakpoint for *Streptococcus anginosus* group (≤0.06 mg/L for susceptible) was utilised for the interpretation of telavancin MIC results obtained against viridans group streptococci, whilst the interpretive criterion for *Streptococcus pyogenes* and *Streptococcus agalactiae* (≤0.12 mg/L for susceptible) was applied for β-haemolytic streptococci [1].

Table 1
Telavancin activity and minimum inhibitory concentration (MIC) distribution against a contemporary (2011–2013) and worldwide collection of clinical isolates.

Genus Group	MIC (mg/L)		No. (cumulative %) inhibited at a telavancin MIC (mg/L) of[a]				
Species (no. tested)	MIC_{50}	MIC_{90}	≤0.015	0.03	0.06	0.12	0.25
Staphylococcus spp. (1656)							
Staphylococcus intermedius (11)	≤0.015	≤0.015	**10 (90.9)**	1 (100.0)			
Staphylococcus lugdunensis (258)	≤0.015	0.03	**147 (57.0)**	98 (95.0)	13 (100.0)		
Staphylococcus hominis (414)	≤0.015	0.06	**228 (55.1)**	127 (85.7)	58 (99.8)	1 (100.0)	
Staphylococcus simulans (48)	0.03	0.06	0 (0.0)	**24 (50.0)**	21 (93.8)	3 (100.0)	
Staphylococcus haemolyticus (425)	0.06	0.06	24 (5.6)	126 (35.3)	**262 (96.9)**	13 (100.0)	
Staphylococcus caprae (42)	0.06	0.06	1 (2.4)	12 (31.0)	**28 (97.6)**	1 (100.0)	
Staphylococcus cohnii (27)	0.06	0.06	1 (3.7)	12 (48.1)	**13 (96.3)**	1 (100.0)	
Staphylococcus capitis (214)	0.06	0.06	24 (11.2)	72 (44.9)	**114 (98.1)**	3 (99.5)	1 (100.0)
Staphylococcus warneri (93)	0.06	0.06	4 (4.3)	31 (37.6)	**51 (92.5)**	7 (100.0)	
Staphylococcus saprophyticus (106)	0.06	0.12	3 (2.8)	4 (6.6)	**58 (61.3)**	39 (98.1)	2 (100.0)
Staphylococcus pettenkoferi (18)	0.06	0.12	0 (0.0)	**8 (44.4)**	4 (66.7)	6 (100.0)	
Viridans group streptococci (1939)							
Streptococcus anginosus group (627)	≤0.015	0.03	**371 (59.2)**	238 (97.1)	18 (100.0)		
Streptococcus anginosus (434)	≤0.015	0.03	**227 (52.3)**	195 (97.2)	12 (100.0)		
Streptococcus constellatus (157)	≤0.015	0.03	**119 (75.8)**	36 (98.7)	2 (100.0)		
Streptococcus intermedius (36)	≤0.015	0.06	**25 (69.4)**	7 (88.9)	4 (100.0)		
Streptococcus mitis group (1039)	≤0.015	0.03	**604 (58.1)**	388 (95.5)	46 (99.9)	1 (100.0)	
Streptococcus mitis/oralis (788)	≤0.015	0.03	**488 (61.9)**	268 (95.9)	31 (99.9)	1 (100.0)	
Streptococcus sanguinis (113)	≤0.015	0.03	**58 (51.3)**	49 (94.7)	6 (100.0)		
Streptococcus gordonii (37)	0.03	0.06	15 (40.5)	**18 (89.2)**	4 (100.0)		
Streptococcus parasanguinis (101)	0.03	0.03	43 (42.6)	**53 (95.0)**	5 (100.0)		
Other viridans group streptococci							
Streptococcus salivarius (123)	≤0.015	0.03	**77 (62.6)**	38 (93.5)	7 (99.2)	1 (100.0)	
Streptococcus vestibularis (10)	≤0.015	≤0.015	**9 (90.0)**	1 (100.0)			
Streptococcus bovis/gallolyticus (126)	0.03	0.03	**61 (48.4)**	59 (95.2)	6 (100.0)		
Streptococcus mutans (14)	0.03	0.06	3 (21.4)	**9 (85.7)**	2 (100.0)		
β-streptococci (157)							
Streptococcus dysgalactiae (143)	≤0.015	0.03	**109 (76.2)**	28 (95.8)	5 (99.3)	1 (100.0)	
Streptococcus equisimilis (14)	≤0.015	0.06	**7 (50.0)**	5 (85.7)	2 (100.0)		
Other genera (69)							
Micrococcus spp. (11)	≤0.015	≤0.015	**11 (100.0)**				
Listeria spp. (24)	≤0.015	0.03	**21 (87.5)**	3 (100.0)			
Corynebacterium spp. (34)	≤0.015	0.03	**29 (85.3)**	4 (97.1)	1 (100.0)		

[a] Modal MIC results are in bold.

Breakpoint criteria for comparator agents were those from the CLSI [9].

3. Results and discussion

Overall, lower telavancin MIC_{50} results were noted against *Staphylococcus hominis* (MIC_{50}, ≤0.015 mg/L), *Staphylococcus intermedius* (MIC_{50}, ≤0.015 mg/L), *Staphylococcus lugdunensis* (MIC_{50}, ≤0.015 mg/L) and *Staphylococcus simulans* (MIC_{50}, 0.03 mg/L) compared with a slightly higher MIC_{50} value obtained against other staphylococcal species (MIC_{50}, 0.06 mg/L) (Table 1). The comparator, daptomycin, also showed a similar activity profile (MIC_{50} values) against staphylococci other than *S. aureus*, with lower MIC_{50} results (0.12–0.25 mg/L) for *S. hominis*, *S. intermedius*, *S. lugdunensis*, *S. simulans* and *Staphylococcus haemolyticus* and higher values (0.5–1 mg/L) against other species (Table 2). Vancomycin showed constant MIC_{50} results (1 mg/L) against CoNS, whilst linezolid MIC_{50} values varied between 0.25 mg/L and 1 mg/L. Telavancin demonstrated MIC_{50} results at least four-fold lower than these comparators when tested against these staphylococci; only one *Staphylococcus capitis* and two *Staphylococcus saprophyticus* (0.2%) had telavancin MIC results (i.e. 0.25 mg/L) above the susceptible breakpoint for *S. aureus* (i.e. ≤0.12 mg/L). These isolates exhibited daptomycin, vancomycin and linezolid MIC values of 0.5–1, 0.5–2 and 0.5–2 mg/L, respectively. In addition, the telavancin MIC_{50} and MIC_{90} results tested against CoNS remained stable (0.03 mg/L and 0.06 mg/L, respectively), regardless of the oxacillin susceptibility status (data not shown).

Viridans group streptococci were very susceptible to telavancin (99.9% susceptible at ≤0.06 mg/L), with MIC_{50} results of ≤0.015 mg/L or 0.03 mg/L (Tables 1 and 2). The comparator agents, vancomycin and linezolid, had MIC_{50} values of 0.5 mg/L and 0.5–1 mg/L, respectively. Daptomycin also showed MIC_{50} results of 0.25 mg/L and 0.5 mg/L, except for *Streptococcus bovis/gallolyticus* (MIC_{50}, ≤0.06 mg/L) and *Streptococcus salivarius/vestibularis* (MIC_{50}, 0.12 mg/L). One *Streptococcus mitis* and one *S. salivarius* had non-susceptible results for telavancin (i.e. MIC, 0.12 mg/L). The *S. mitis* displayed MIC values of 2, 1 and 1 mg/L for daptomycin, vancomycin and linezolid, respectively, whilst the *S. salivarius* strain exhibited MIC results 0.12, 0.5 and 1 mg/L, respectively (data not shown).

Telavancin (MIC_{50}, ≤0.015 mg/L) and daptomycin (MIC_{50}, ≤0.06 mg/L) showed greatest activities against *Streptococcus dysgalactiae* and *Streptococcus equisimilis*, followed by vancomycin (MIC_{50}, 0.25 mg/L) and linezolid (MIC_{50}, 1 mg/L) (Tables 1 and 2). These four agents also inhibited all β-haemolytic streptococci at or below their respective applied breakpoints for susceptibility

Table 2
Antimicrobial activity and spectrum of telavancin and comparator agents against a worldwide collection of clinical isolates.

Genus	MIC_{50}, MIC_{90} (mg/L) and % susceptible[a] for each agent											
Group	Telavancin			Vancomycin			Daptomycin			Linezolid		
Species (no. tested)	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S
Staphylococcus spp. (1656)												
Staphylococcus intermedius (11)	≤0.015	≤0.015	100.0	1	1	100.0	0.12	0.25	100.0	0.5	1	100.0
Staphylococcus lugdunensis (258)	≤0.015	0.03	100.0	1	1	100.0	0.25	0.25	100.0	0.5	0.5	100.0
Staphylococcus hominis (414)	≤0.015	0.06	100.0	1	2	100.0	0.25	0.5	100.0	0.5	1	99.8
Staphylococcus simulans (48)	0.03	0.06	100.0	1	1	100.0	0.25	0.5	100.0	1	1	97.9
Staphylococcus haemolyticus (425)	0.06	0.06	100.0	1	2	100.0	0.25	0.5	100.0	0.5	1	99.5
Staphylococcus caprae (42)	0.06	0.06	100.0	1	1	100.0	0.5	0.5	100.0	0.5	1	100.0
Staphylococcus cohnii (27)	0.06	0.06	100.0	1	1	100.0	0.5	0.5	100.0	1	2	96.3
Staphylococcus capitis (214)	0.06	0.06	99.5	1	1	100.0	0.5	1	99.5	0.5	1	99.1
Staphylococcus warneri (93)	0.06	0.06	100.0	1	2	100.0	0.5	1	100.0	0.5	1	100.0
Staphylococcus saprophyticus (106)	0.06	0.12	98.1	1	2	100.0	0.5	0.5	100.0	1	1	100.0
Staphylococcus pettenkoferi (18)	0.06	0.12	100.0	1	2	100.0	1	2	83.3	0.25	0.5	100.0
Viridans group streptococci (1939)												
Streptococcus anginosus group (627)	≤0.015	0.03	100.0	0.5	1	100.0	0.25	0.5	99.8	1	1	100.0
Streptococcus anginosus (434)	≤0.015	0.03	100.0	0.5	1	100.0	0.25	0.5	99.8	1	1	100.0
Streptococcus constellatus (157)	≤0.015	0.03	100.0	0.5	1	100.0	0.25	0.5	100.0	0.5	1	100.0
Streptococcus intermedius (36)	≤0.015	0.06	100.0	0.5	1	100.0	0.25	0.5	100.0	0.5	1	100.0
Streptococcus mitis group (1039)												
Streptococcus gordonii (37)	0.03	0.06	100.0	0.5	0.5	100.0	0.5	1	100.0	0.5	1	100.0
Streptococcus mitis/oralis (788)	≤0.015	0.03	99.9	0.5	0.5	100.0	0.5	1	99.2	0.5	1	100.0
Streptococcus parasanguinis (101)	0.03	0.03	100.0	0.5	0.5	100.0	0.5	1	98.0	1	1	100.0
Streptococcus sanguinis (113)	≤0.015	0.03	100.0	0.5	0.5	100.0	0.25	0.5	100.0	0.5	1	99.1[b]
Other viridans group streptococci												
Streptococcus bovis/gallolyticus (126)	0.03	0.03	100.0	0.5	0.5	100.0	≤0.06	0.12	100.0	1	1	100.0
Streptococcus mutans (14)	0.03	0.06	100.0	0.5	1	100.0	0.25	0.5	100.0	0.5	1	100.0
Streptococcus salivarius (123)	≤0.015	0.03	99.2	0.5	1	100.0	0.12	0.25	100.0	0.5	1	100.0
Streptococcus vestibularis (10)	≤0.015	≤0.015	100.0	0.5	0.5	100.0	0.12	0.25	100.0	0.5	1	100.0
β-Haemolytic streptococci (157)												
Streptococcus dysgalactiae (143)	≤0.015	0.03	100.0	0.25	0.5	100.0	≤0.06	0.12	100.0	1	1	100.0
Streptococcus equisimilis (14)	≤0.015	0.06	100.0	0.25	0.5	100.0	≤0.06	≤0.06	100.0	1	1	100.0
Other genera (69)												
Corynebacterium spp. (34)	≤0.015	0.03	–[c]	0.25	0.5	–	≤0.06	0.25	–	0.25	0.5	–
Listeria spp. (24)	≤0.015	0.03	–	1	1	–	2	4	–	1	2	–
Micrococcus spp. (11)	≤0.015	≤0.015	–	0.25	0.25	–	0.12	0.25	–	0.5	0.5	–

[a] Breakpoint criteria for telavancin according to the labelling supplement for the product VIBATIV®, as available. The US Food and Drug Administration (FDA)-approved breakpoint for telavancin against *S. aureus* (≤12 mg/L for susceptible) was used for staphylococci. The breakpoint for viridans group streptococci was that from *S. anginosus* group (≤0.06 mg/L for susceptible), whilst the interpretive criterion for *S. pyogenes* and *S. agalactiae* (≤0.12 mg/L for susceptible) was applied for other β-haemolytic streptococci [1]. Breakpoint criteria for comparator agents were those from the Clinical and Laboratory Standards Institute (CLSI) [9].
[b] One *S. sanguinis* with a linezolid MIC of 32 mg/L [11].
[c] Breakpoint not available.

(Table 2). Other tested genera such as *Micrococcus* spp. ($MIC_{50/90}$, ≤0.015/≤0.015 mg/L), *Listeria* spp. ($MIC_{50/90}$, ≤0.015/0.03 mg/L) and *Corynebacterium* spp. ($MIC_{50/90}$, ≤0.015/0.03 mg/L) showed telavancin MIC_{100} results of ≤0.015, 0.03 and 0.06 mg/L, respectively (Table 1).

Because the reference broth microdilution method for telavancin susceptibility testing was revised, this study was intended to update the in vitro information and to re-establish the benchmark for telavancin when tested against these uncommon isolates. The species or group of species presented here also include primary (i.e. *S. anginosus* group) and secondary (i.e. *S. haemolyticus* and *S. dysgalactiae*) indicated organisms [1]. In addition, these in vitro data confirm the activity and spectrum of telavancin against these less commonly encountered Gram-positive species, and report telavancin potency greater than three comparator agents (daptomycin, linezolid and vancomycin) with clinical indications for treatment of uncomplicated and complicated SSTI.

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Competing interest

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Ethical approval

Not required.

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